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Highlights

- We investigated hippocampal and parietal contributions to VSTM development
- Children recruited the posterior hippocampus during successful VSTM processing
- Adults showed a functional specialization in the anterior hippocampus
- Parietal activity linearly increased across the full developmental trajectory
- Age related improvements in VSTM was explained by a hippocampal-parietal network

Title:

Hippocampal and posterior parietal contributions to developmental increases in visual short-term memory capacity

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Abstract:

Developmental increases in visual short-term memory (VSTM) capacity have been associated with changes in attention processing limitations and changes in neural activity within neural networks including the posterior parietal cortex (PPC). A growing body of evidence suggests that the hippocampus plays a role in VSTM, but it is unknown whether the hippocampus contributes to the capacity increase across development. We investigated the functional development of the hippocampus and PPC in 57 children, adolescents and adults (age 8-27 years) who performed a visuo-spatial VSTM-match-to-sample change detection task. A negative relationship between age and VSTM related activity was found in the right posterior hippocampus that was paralleled by a positive age-activity relationship in the right PPC. In the posterior hippocampus, VSTM related activity predicted individual capacity in children, whereas neural activity in the right anterior hippocampus predicted individual capacity in adults. ~~Furthermore, neural activity in the anterior hippocampus and the PPC were inversely related to each other in low capacity individuals, which became most evident by adulthood.~~ The findings provide first evidence that VSTM development is supported by an integrated neural network that involves hippocampal and posterior parietal regions.

Key words:

visual short-term memory, hippocampus, posterior parietal cortex, development, individual differences

1. Introduction

The amount of information that can be held in visual short-term memory (VSTM) is known to increase substantially from childhood through early adulthood (Gathercole, 1999; Pickering, Gathercole, Hall, & Lloyd, 2001). The majority of evidence suggests that these improvements depend on changes in attention processing limitations and associated neural networks that include the posterior parietal cortex (PPC) (Klingberg, Forssberg, & Westerberg, 2002; Klingberg, 2006; Olesen, Nagy, Westerberg, & Klingberg, 2003). These changes, however, do not serve as a sufficient explanation for age related capacity increases as suggested by behavioral and psychophysiological studies (Astle et al., 2014; Cowan, Morey, AuBuchon, Zwilling, & Gilchrist, 2010). Instead, other cognitive processes and brain regions might additionally explain developmental improvements in VSTM capacity, which is to date unclear.

In the adult cognitive neuroscience literature, a growing body of research points to a role of the hippocampus in working memory (Finke et al., 2008; Hannula & Ranganath, 2008; Olson, Page, Moore, Chatterjee, & Verfaellie, 2006; Piekema, Kessels, Mars, Petersson, & Fernández, 2006). This idea was supported by recent evidence that neural activity in the hippocampus predicted individual VSTM capacity (von Allmen, Wurmitzer, Martin, & Klaver, 2013). In that study, participants performed a visuo-spatial ~~match-to-sample~~change detection task during blood oxygenation level dependent (BOLD) fMRI scanning. In high capacity individuals, neural activity in the hippocampus incrementally increased up to set size six, whereas low capacity individuals showed a drop in hippocampal activity when their capacity limit had been exceeded. Within the present study, we aimed to substantiate our previous findings by testing the hippocampus' contribution to VSTM across development. In particular, we asked whether VSTM capacity is predicted by neural activity within the

hippocampus across development and whether age related differences in hippocampal activity are linked to developmental increases in VSTM capacity.

In light of the development of the hippocampus, recent studies demonstrated age related structural and functional changes along its longitudinal axis (DeMaster & Ghetti, 2013; DeMaster, Pathman, Lee, & Ghetti, 2013; Ghetti, DeMaster, Yonelinas, & Bunge, 2010; Gogtay et al., 2006). Gogtay et al. (2006) for example reported developmental changes in gray matter volume along the hippocampal anterior-posterior axis, whereas its total volume remained constant. Furthermore, correct episodic retrieval of relational information in adults was associated with neural activity in the anterior hippocampus, whereas children showed the same pattern specifically in the posterior hippocampus (DeMaster & Ghetti, 2013). Together, these findings provide evidence for regional age related changes in the hippocampus that might be as well related to simultaneously occurring progressive and regressive events along its longitudinal axis. Two further questions, therefore, were whether the anterior and posterior hippocampus show different developmental trajectories within the framework of VSTM and whether a possible regressive event in the posterior hippocampus parallels a progressive one in the anterior hippocampus with respect to a posterior-to-anterior shift.

In contrast to the sparse evidence for the role of the hippocampus in VSTM, it is well established that individual and developmental differences in VSTM capacity depend on neural activity in the PPC (Fukuda & Vogel, 2009; Klingberg et al., 2002; Magen, Emmanouil, McMains, Kastner, & Treisman, 2009; Olesen, Macoveanu, Tegnér, & Klingberg, 2007; Vogel, McCollough, & Machizawa, 2005). Another important question can hence be raised whether age related improvements in VSTM capacity may result from an integrated neural network that covers both the hippocampus and the PPC. In this context, we also intended to corroborate previous studies that

reported age differences in working memory activity in the recruitment of the PPC (e.g., Klingberg et al., 2002).

In order to examine these questions, we measured BOLD fMRI in a priori defined subregions in the left/right hippocampus (head, anterior body, posterior body and tail) and PPC in three different age groups (children, adolescents and adults) during the completion of a visuo-spatial match-to-sample change detection task. Similar tasks have been used to probe set size modulated brain activity within VSTM (Todd & Marois, 2004; Vogel & Machizawa, 2004), or to demonstrate that damaged hippocampus affected processing of object-location associations (Finke et al., 2008; Olson et al., 2006).

2. Materials and Methods

2.1. Participants

Data were collected from 21 adults (age 19-27 years, mean = 22.2 ± 2.19 years, nine males), 16 adolescents (age 13-17 years, mean = 15.2 ± 1.47 years, six males) and 20 children (age 8-12 years, mean = 10.0 ± 1.34 years, nine males), after giving informed consent according to procedures approved by the Cantonal Ethics Committee Zurich. All participants were German speaking, had normal or corrected-to-normal vision and had no history of neuropsychiatric disorders. Age groups were comparable in terms of their socioeconomic status (educational level of both parents) and did not differ in a common estimate of general nonverbal intelligence (Matrix Reasoning) and an assorted subtest for verbal intelligence (Similarities) that were assessed with the German versions of the Wechsler Intelligence Scale for Children (HAWIK-IV; Petermann and Petermann, 2007) and Wechsler Adult Intelligence Scale (WIE; Wechsler and von Aster, 2009) (data not shown). Additional data from seven

children and three adolescents were excluded due to head motion during scanning that exceeded 3 mm, or because of failing to follow the instructions (one child). Within the adult group, we reanalyzed data of the same individuals previously examined (von Allmen et al., 2013).

2.2. Task design

Before beginning the measurement, all participants were trained to perform the task on trials that were not included in the actual task. Fig. 1A shows a sample of a trial used in our match-to-sample change detection task that required encoding, maintenance and retrieval of colored squares, spatially arranged within arrays of different set size conditions. Each trial started with a presentation of a central fixation cross on a light gray background (2000 ms). Then, an array of one, two, four or six objects was presented (800 ms). Subjects were instructed to retain these objects over a short period (900 ms). Finally, a probe array appeared (2000 ms), whereon subjects indicated by button press whether or not the probe matched the study array. A mismatch was introduced by a change of color in one square, while stimulus locations were held constant within a trial. Responses were given with index fingers of the left and right hand. Left-right allocation of response types (match/mismatch) was counterbalanced across subjects. Eighty trials in four set size conditions (20 trials per set size condition, 50% matches) and 24 null events (3500 ms, fixation cross) were randomly intermixed over the entire scanning session. Each trial onset was jittered with a variable inter-stimulus interval (8 x 0 ms, 6 x 1000 ms, 4 x 2000 ms and 2 x 3000 ms per set size condition).

2.3. Image Acquisition

Whole brain functional images were acquired using conventional techniques on a 3-T GE MRI scanner (GE Medical Systems, Milwaukee, WI). Following four dummy scans, 354 T2*-weighted echo-planar imaging (EPI) scans were collected using an interleaved acquisition sequence (35 axial slices 15° to the AC-PC line, 3.13 x 3.13 mm² in plane, TR = 1.9 s, TE = 32 ms, 75° flip-angle, matrix = 64 x 64, slice thickness = 3 mm, slice gap = 0.3 mm). For task presentation, we used a Dell Precision M70 laptop running with Presentation 11 (Neurobehavioral Systems, Albany, CA) for Windows. The stimuli were back-projected on a screen viewed by the subject through a prism mirror.

2.4. fMRI analysis

Functional MRI data were processed and analyzed using Statistical Parametric Mapping (SPM8; Wellcome Trust Centre for Neuroimaging, London). All volumes were first corrected for slice acquisition timing and realigned to the first image for motion correction using rigid body realignment. Imaging data were then spatially normalized to the Montreal Neurological Institute (MNI) template brain (voxel size = 3 x 3 x 3). The use of a common adult template has been validated for children aged 7 years and older (Burgund et al., 2002; Kang, Burgund, Lugar, Petersen, & Schlaggar, 2003). To obtain hemodynamic response at stimulus onset for each event type, a canonical hemodynamic response function (HRF; Friston et al., 1998) and its temporal derivative were modelled. The events of interest were locked to the onset of sample arrays (duration = 3700 ms; onset sample array until end probe array). Four regressors modelled neural responses of the set size conditions. One additional regressor was used to model HRF related to incorrect trials (not considered in following statistical analyses) and additional 24 movement regressors were used to control for motion-correlated activity (implemented as multiple regressors within first

level analyses). These included the standard 6 motion regressors, for translation (x, y and z) and for rotation (pitch, roll and yaw) with and without their temporal derivatives, plus their quadratic term with and without their temporal derivatives.

Regions of interest (ROI) analyses were performed with respect to our regional specific hypothesis regarding the hippocampus and PPC. Since evidence exists of developmental changes in the functional organization along the longitudinal axis of the hippocampus (DeMaster & Ghetti, 2013; Ghetti et al., 2010), we divided the left and right hippocampal ROI (provided by the AAL atlas) into eight non-overlapping subregions: left/right head, anterior body, posterior body and tail, using predefined Y-coordinates (DeMaster & Ghetti, 2013). A priori areas in the PPC were defined as spheres (radius = 8 mm) with the center at coordinates reported by Todd and Marois (2004) (left/right PPC, -22/23 -65/-59 42/45). We decided to adopt the coordinates from Todd and Marois due to the content related proximity to their approach. Percentage signal change estimates for each set size condition were extracted from the ROIs using MarsBar toolbox for SPM (Brett, Anton, Valabregue, & Poline, 2002). Visual short-term memory related activity was operationalized as the activation difference between large (4 and 6) and small (1 and 2) set sizes ($S_{\text{large}} - S_{\text{small}}$). Within each ROI, a multiple regression analysis was performed in SPSS 22.0 (IBM, Armonk, NY) with the dependent variable $S_{\text{large}} - S_{\text{small}}$ and the factors age and K_{max} . The interaction term $\text{age} * K_{\text{max}}$ was included as a third predictor.

3. Results

3.1. Behavioral results

VSTM capacity was estimated by Cowan's K-formula (Cowan, 2001): $K = (\text{hit rate} + \text{correct rejection rate} - 1) N$, where N is the number of objects presented, by

assigning the maximal K-score over all set size conditions (K_{\max}). A hit was defined as a correctly identified mismatch. Across all 57 participants, K_{\max} ranged from 2 to 6 objects ($M = 4.01$, $SD = .92$; detailed results are listed in Table 1). As expected, a positive correlation was found between age and K_{\max} ($r = .40$, $p = .002$) (Fig. 1B). In adults and adolescents, K_{\max} correlated with ~~correct rejection~~hit rate at large set sizes (4 and 6) (adults, $r = .71$, $p < .001$; adolescents, $r = .92$, $p < .001$; children, $r = .39$, $p = .092$), while a similarly strong correlation between K_{\max} and ~~hit~~correct rejection rate at large set sizes was observed exclusively in children (children, $r = .78$, $p < .001$; adolescents, $r = .54$, $p = .033$; adults, $r = .36$, $p = .106$).

3.2. fMRI results

The multiple regression analyses for each hippocampal ROI revealed a significant relationship between K_{\max} and $S_{\text{large}} - S_{\text{small}}$ in the left and right hippocampal tail (left tail, $\beta = .32$, $p = .024$; right tail, $\beta = .35$, $p = .012$). As can be seen in Fig. 2A, $S_{\text{large}} - S_{\text{small}}$ in both of these regions ranged from negative in low capacity individuals to positive in high capacity individuals, indicating a relative decrease in hippocampal activity at larger set sizes in low capacity individuals and a relative increase in hippocampal activity at larger set sizes in high capacity individuals.

To test for a hippocampal contribution to developmental improvements in VSTM capacity, we included age and age* K_{\max} as further predictors within the regression models. This revealed a significant relationship between age and $S_{\text{large}} - S_{\text{small}}$ in the right hippocampal tail ($\beta = -.30$, $p = .033$). The negative direction of the regression coefficient indicates that VSTM related activity became smaller with increasing age (Fig. 2A). Note that this linear relationship is independent of individual capacity and purely age related. Similarly, a trend to significance was found for a negative age-activity relationship in the left hippocampal tail ($\beta = -.25$, $p = .070$) (see also Table 2).

Together, the data so far showed that a negative age-activity relationship in the posterior hippocampus was paralleled by a positive capacity-activity relationship in the same hippocampal subregion. The interaction term $\text{age} \times K_{\max}$ was as well a significant predictor for $S_{\text{large}} - S_{\text{small}}$ in the left and right posterior hippocampus (left tail, $\beta = -.26$, $p = .044$; right tail, $\beta = -.27$, $p = .034$). To better understand these interaction effects, we calculated post-hoc correlations between K_{\max} and $S_{\text{large}} - S_{\text{small}}$ in the left and right hippocampal tail separately within each age group. This revealed a significant result only in children (left tail, $r = .69$, $p = .001$; right tail, $r = .75$, $p < .001$). Since in our previous study, individual capacity predicted VSTM related activity in bilateral anterior hippocampus (MNI coordinates for left/right hippocampus, -36/39 -16/-13 -17/-23) in adults (von Allmen et al., 2013), we calculated capacity-activity correlations for each age group in the left/right hippocampal head. This pointed to a significant result only in the adult's right head ($r = .55$, $p = .010$) (for detailed results, see supplementary information, Table A). In the right hippocampus, a functional specialization of the head was observed exclusively in adults, whereas children predominately recruited the tail during successful VSTM processing (Fig. 3).

Due to developmental structural changes across the hippocampal longitudinal axis (Gogtay et al., 2006), our data might have depended on regional age related power differences. For that reason, we recalculated the regression analyses within each hippocampal ROI with an additional predictor of individual regional gray matter volume. Most importantly, regression coefficients and p -values for age, K_{\max} and $\text{age} \times K_{\max}$ did not markedly change in left and right hippocampal tail after holding individual differences in regional gray matter volume constant (see supplementary information, Table B).

In addition to the hippocampus, we investigated age related differences in the recruitment of the PPC. Two regression analyses (i.e., for the left/right PPC ROI) were conducted with the three predictors used above (age, K_{\max} and age* K_{\max}). Age was a significant predictor for $S_{\text{large}} - S_{\text{small}}$ in the right PPC ($\beta = .44$, $p = .002$). No reliable effects were found with respect to capacity related VSTM activity (i.e., K_{\max} and age* K_{\max} were no significant predictors for $S_{\text{large}} - S_{\text{small}}$, Table 2).

So far, neural activity increased with age in the right PPC and decreased with age in the right posterior hippocampus. In order to consolidate a potential hippocampus-to-PPC shift across development, we applied a more strict analysis, which tested for an inverse relationship between these two regions mediated by age using the INDIRECT macro for SPSS (www.afhayes.com). That is, we asked whether $S_{\text{large}} - S_{\text{small}}$ in the hippocampal tail (ROI1) predicted $S_{\text{large}} - S_{\text{small}}$ in the PPC (ROI2) through the mediator age (a conceptual diagram is shown in Fig. 1C). Because this test builds on the pure age related effects, which were independent of individual capacity, we included the covariate K_{\max} . The same procedure was applied to additionally test for a head-to-PPC and a tail-to-head shift. To avoid power differences due to different ROI volumes (left/right PPC, 2240/2240 mm²; head, 3728/3608 mm²; tail, 1376/1528 mm²), we defined the left/right anterior and posterior hippocampal ROIs as spheres with a radius of 8 mm (i.e., same radius as for the PPC sphere) at the center of mass of the original head and tail ROIs. No reliable effects were found for interregional relationships mediated by age. As can be seen in Table 3, $S_{\text{large}} - S_{\text{small}}$ in the left PPC inversely related to $S_{\text{large}} - S_{\text{small}}$ in the left hippocampal head ($\beta = -.49$, $p = .036$), which was independent of age (and K_{\max}). Furthermore, the effect of $S_{\text{large}} - S_{\text{small}}$ in the right tail to age (path a) and the direct effect of age on $S_{\text{large}} - S_{\text{small}}$ in the right PPC (path b) were in line with the preceding findings.

Finally, since we found a capacity-activity correlation in the hippocampal tail only in children and a similar effect in the right head only in adults, we aimed to further substantiate a possible anterior hippocampal specialization across development. That is, we tested for a conditional effect of $S_{\text{large}} - S_{\text{small}}$ in the tail (ROI1) on $S_{\text{large}} - S_{\text{small}}$ in head (ROI2) for different values of age and K_{max} (a conceptual diagram is shown in Fig. 1C). This moderation analysis was performed with the PROCESS v2.11 macro for SPSS (www.afhayes.com) using the ROIs of equal volume. The same procedure was again applied to additionally test for interregional relationships within a hippocampal-parietal network. An overview of the results is shown in Table 4. Most notably, we found a trend to significance for a 3-way interaction between $S_{\text{large}} - S_{\text{small}}$ in the right hippocampal head, K_{max} and age in the prediction of $S_{\text{large}} - S_{\text{small}}$ in the right PPC ($\beta = .09, p = .098$) (a detailed listing of the output of the PROCESS macro is shown in the supplementary information, Table C). At the highest age value of 21.49 years specified by PROCESS, there was a significant relationship between the interaction term $S_{\text{large}} - S_{\text{small}}$ in the right hippocampal head* K_{max} and $S_{\text{large}} - S_{\text{small}}$ in the right PPC ($\beta = .99, p = .039$). At this age, $S_{\text{large}} - S_{\text{small}}$ in the right head predicted $S_{\text{large}} - S_{\text{small}}$ in the right PPC only at the lowest K_{max} value of 3.09 ($\beta = -1.52, p = .050$). Low capacity in adults was thus associated with an inverse relationship between VSTM activity in the right PPC and the right anterior hippocampus. At the moderate age value of 15.97 years, there was a similar negative relationship between $S_{\text{large}} - S_{\text{small}}$ in the right head and $S_{\text{large}} - S_{\text{small}}$ in the right PPC near significance at the lowest K_{max} value of 3.09 ($\beta = -.83, p = .059$). It should be however mentioned that the relationship between the interaction term $S_{\text{large}} - S_{\text{small}}$ in the right hippocampal head* K_{max} and $S_{\text{large}} - S_{\text{small}}$ in the right PPC was not significant at this age ($\beta = .47, p = .149$). Following the same approach, no reliable results were found for the conditional effects of $S_{\text{large}} - S_{\text{small}}$ in the tail on $S_{\text{large}} - S_{\text{small}}$

~~S_{small} in the head and the PPC (Table 4). Taken together, this moderation analysis revealed an inverse relationship between VSTM activity in the anterior hippocampus and the PPC in low capacity individuals, which became most evident by adulthood. At the neural network level, a functional specialization of the anterior hippocampus thus involved the PPC.~~

4. Discussion

The present study aimed to investigate the neural bases of developmental improvements in VSTM capacity. Building on our previous study in adults (von Allmen et al., 2013), we first asked whether VSTM capacity related to hippocampal activity across the full developmental trajectory. We found a positive relationship between individual VSTM capacity and neural activity in bilateral posterior hippocampus. In particular, higher memory capacity was associated with a relative increase in neural activity at larger set sizes, while a decrease in activity was observed in low capacity individuals. In low capacity individuals, a drop in neural activity at larger set sizes suggests that the hippocampus stopped being involved in successful VSTM processing beyond capacity limit. This is in line with our previous study in adults (von Allmen et al., 2013) and contrasts with previous criticisms that hippocampal activity within short-term memory experiments actually emerged above capacity limit associated with long-term memory functions (Jeneson & Squire, 2012; Jeneson, Wixted, Hopkins, & Squire, 2012). Our findings therefore corroborate the view of a hippocampus' role in working memory (Finke et al., 2008; Hannula & Ranganath, 2008; Nee & Jonides, 2013; Olson et al., 2006; Piekema et al., 2006), i.e., by demonstrating its extent of validity for the first time across development.

The second question was whether age related differences in hippocampal activity were associated with developmental increases in VSTM capacity. Along with the

positive capacity-activity relationship in bilateral hippocampal tail, we found a negative age-activity relationship in the right tail, suggesting that the role of the posterior hippocampus in successful VSTM processing becomes continuously less important with increasing age. Consistently, the interaction term $\text{age} * K_{\max}$ was a significant predictor for neural activity in this region. In other words, the positive relationship between individual capacity and neural activity was moderated by age, which further pointed to a strong capacity-activity correlation only in children. A posterior hippocampal involvement in successful VSTM processing thus was a particular feature in this age group. Unexpectedly, VSTM related activity in the anterior hippocampus was not predicted by age and individual capacity when tested linearly across the full developmental trajectory. However, when tested for a capacity-activity correlation separately within each age groups, individual capacity predicted neural activity in the right hippocampal head exclusively in adults, suggesting an anterior hippocampus' involvement in successful VSTM not before early adulthood. Together with the strong positive age-capacity correlation, the current findings implicate a functional specialization in the adult anterior hippocampus associated with increased VSTM capacity and an initially predominant recruitment of the posterior hippocampus in childhood, which is in line with a recent study that showed a similar differentiation along the anterior-posterior axis of the hippocampus associated with differences in episodic retrieval between children and adults (DeMaster & Ghetti, 2013).

Regarding the involvement of the PPC in VSTM development, we found a positive age-activity relationship, which is in line with the existing developmental literature (Klingberg et al., 2002; Klingberg, 2006; Olesen et al., 2007). However, in contrast to for example Klingberg et al. (2002), our data did not show that an age-activity relationship in this region was paralleled with a capacity-activity relationship. There is

substantial evidence that the PPC is specifically involved in VSTM when attentional processes are required (Bledowski, Rahm, & Rowe, 2009; Magen et al., 2009; Nee & Jonides, 2013). Hence, since our task was not designed to compare different levels of attentional demands, we refrain from further conclusions that an age related parietal contribution to VSTM is independent of individual capacity differences.

Development of working memory may be as well associated with a functional shift from the hippocampus to cortical regions, e.g., from the anterior hippocampus to prefrontal regions (Finn, Sheridan, Kam, Hinshaw, & D'Esposito, 2010). Because a negative age-activity relationship in the posterior hippocampus paralleled a positive one in the PPC, we probed whether these regions were inversely related to each other with respect to a possible developmental hippocampus-to-PPC shift. This analysis showed no reliable age-mediated interregional relationships, which could have further consolidated a functional shift from the posterior hippocampus to the

PPC. ~~To substantiate the relationships between age, capacity and neural activity in the hippocampal head, tail and the PPC, we finally performed additional moderation analyses that tested for the conditional effect of VSTM related activity in one region on VSTM related activity in another region for different values of age and individual capacity. This revealed a significant interaction between right anterior hippocampal activity, individual capacity and age in the prediction of VSTM related activity in the right PPC, which further pointed to an inverse relationship between these two regions in adult low capacity individuals. Since in those individuals an anterior hippocampal involvement in VSTM dropped at larger set size conditions, we can infer that this was directly linked to a greater contribution of posterior parietal mechanisms. At the neural network level, these data thus provide additional evidence that an age related specialization of the anterior hippocampus involved the PPC as anterior hippocampal mechanisms reached their limits. No interregional capacity-activity relationships were~~

~~found in children, suggesting that, within our study, successful VSTM processing predominantly relied on the posterior hippocampus at this age.~~

Do capacity and age related changes in activity within the hippocampus explain an age related increase in VSTM capacity? The current results showed that VSTM related activity in the right posterior hippocampus was not only negatively related to age but as well to individual capacity in children. In adults, individual VSTM capacity predicted neural activity in the anterior hippocampus. Neural activity in the anterior hippocampus has been associated with novelty processing (Düzel et al., 2003; Köhler, Danckert, Gati, & Menon, 2005; Pihlajamäki et al., 2004; Ranganath & D'Esposito, 2001; Sperling et al., 2001), whereas the posterior hippocampus was specifically involved in processing of spatial relations (Nadel, Hoscheidt, & Ryan, 2012; Pihlajamäki et al., 2004). Both novelty detection and spatial processing play an important role in VSTM. First, according to the Feature Integration Theory (Wheeler & Treisman, 2002), whole-display recognition trials probe change-detection (i.e., the detection of a novel item in a probe array), especially during the processing of object-location associations. Second, VSTM stores integrated representations of object features including their spatial locations and spatial relations (Bengson & Mangun, 2011; Klaver, Smid, & Heinze, 1999; Pertzov & Husain, 2013; Treisman & Zhang, 2006). We therefore suppose that the anterior hippocampal engagement might have reflected processing limitations in change-detection abilities that seemed to gain in importance with increasing age for differentiating between high and low capacity individuals. Consistently, our data show a strong positive correlation between mean ~~correct rejection~~hit rate at larger set sizes and individual capacity in adults and adolescents. In contrast, individual differences in children's VSTM capacity might have predominantly relied on spatial processing limitations, which was paralleled by a strong positive correlation between mean ~~hit~~correct rejection rate at larger set sizes

and individual capacity. It is, however, important to note that since our task did not dissociate between novelty detection and spatial processing, first hand evidence will be required to substantiate our hypothesis of a functional dissociation between the anterior and posterior hippocampus.

To our knowledge, this is the first study to show that VSTM capacity is predicted by neural activity within the hippocampus across development. The data furthermore suggest a functional specialization of the anterior hippocampus by early adulthood, ~~which additionally involved the PPC with increasing age,~~ whereas children predominantly recruited the posterior part of the hippocampus during successful VSTM processing. The present study complements the widely acknowledged parietal contribution to working memory development by pointing to an additional involvement of the hippocampus. ~~possible functional dissociation along the hippocampal anterior-posterior axis.~~

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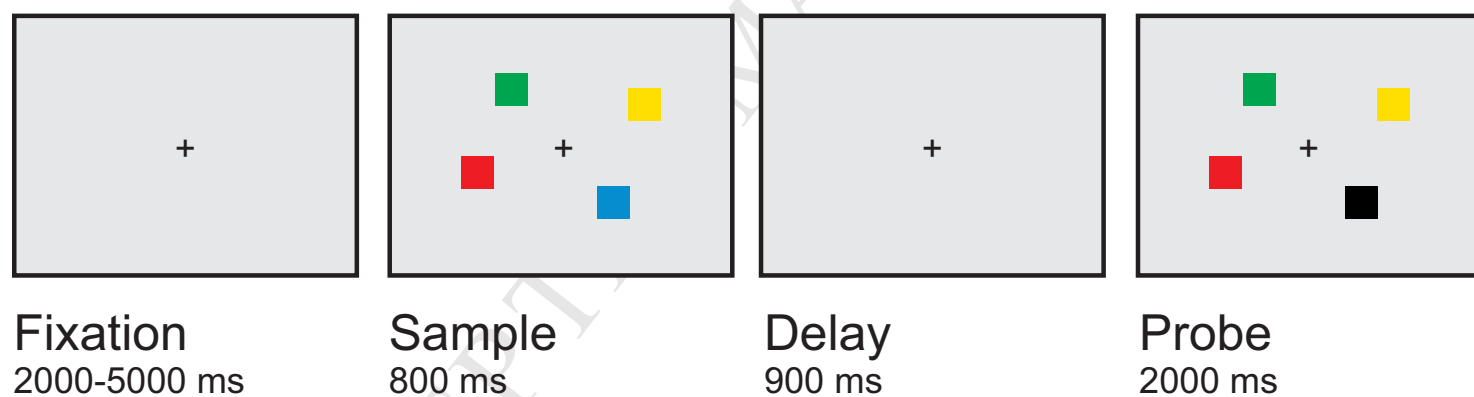
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Figure 1. (A) Example of the visuo-spatial match-to-sample change detection task (mismatch trail). Participants were instructed to hold sample arrays consisting of one, two, four, or six colored squares for brief periods of time. By the presentation of the probe array, a match or mismatch response was required. (B) Correlation between age and K_{\max} across the full developmental range. (C) Conceptual designs for the mediation ~~(top) and moderation (bottom)~~ model. The mediation analysis tested for a linear relationship between two regions (ROI1 and ROI2) mediated by age. Individual VSTM capacity was included as a covariate. ~~The moderation analysis tested for a conditional effect of neural activity in one region (ROI1) on neural activity in another region (ROI2) for different values of age and K_{\max} .~~

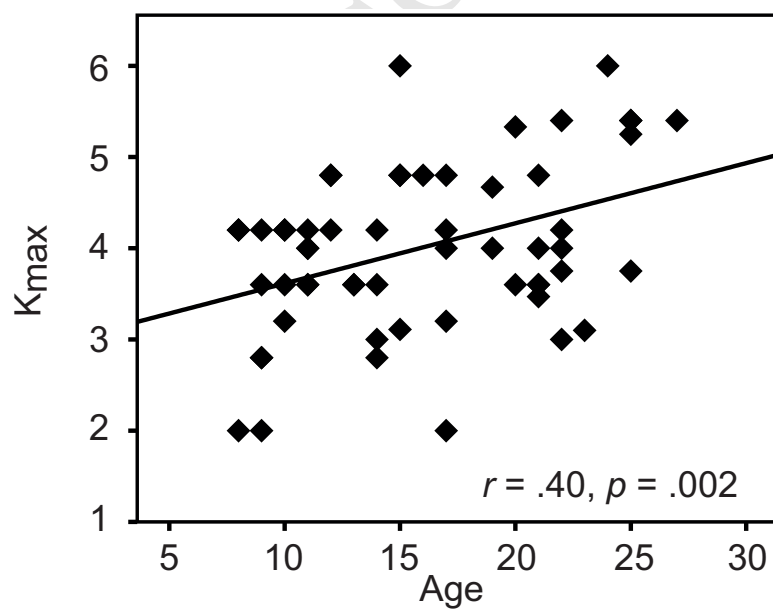
Figure 2. Linear relationships between $S_{\text{large}} - S_{\text{small}}$ and K_{\max} (top) and age (bottom) for (A) the left and right hippocampal tail and (B) right PPC. For β and corresponding p -values, see Table 2.

Figure 3. Correlations between K_{\max} and $S_{\text{large}} - S_{\text{small}}$ in the right hippocampal head and tail for adults and children. For r and corresponding p -values, see Table A (supplementary information).

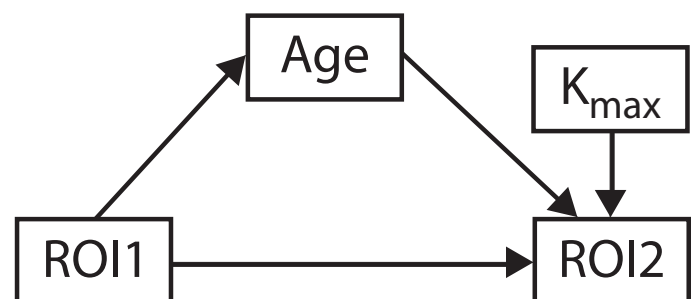
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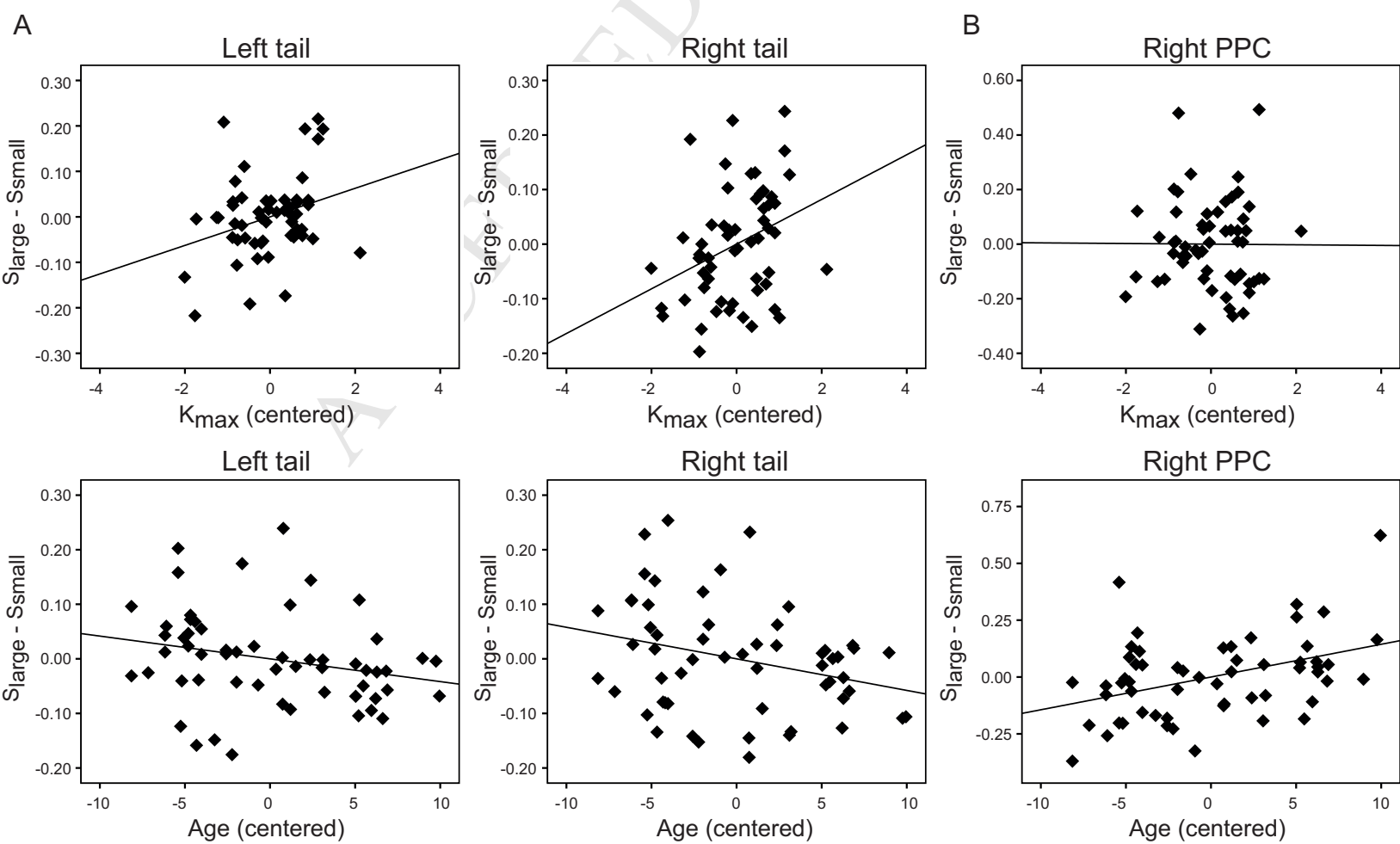


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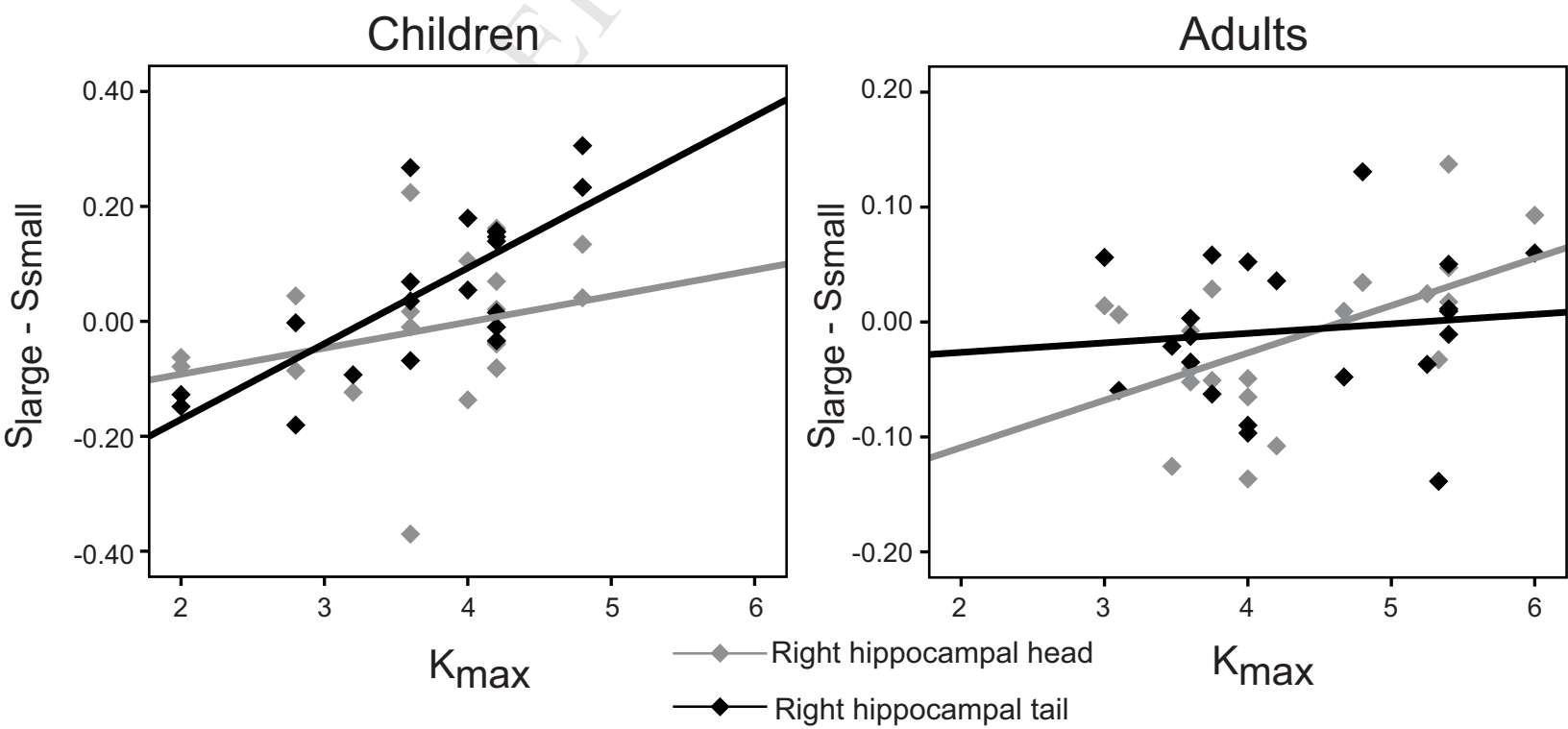


Table 1.VSTM capacity (K_{\max}) across age groups.

	Mean Kmax \pm SD	MIN	MAX
Adults	4.37 \pm 0.90	3.00	6.00
Adolescents	3.91 \pm 1.00	2.00	6.00
Children	3.71 \pm 0.80	2.00	4.80

Table 2.

Multiple regression analyses within the hippocampal and posterior parietal ROIs.

$S_{\text{large}} - S_{\text{small}}$	R^2		Age		K_{max}		Age* K_{max}	
	R^2	p	β	p	β	p	β	p
Left hippocampus								
Head	.02	.783	-.10	.492	.12	.424	-.07	.599
Anterior body	.03	.642	-.11	.452	.04	.780	.15	.275
Posterior body	.02	.777	-.02	.890	.00	.980	-.14	.317
Tail	.16	.023	-.25	.070	.32	.024	-.26	.044
Right hippocampus								
Head	.01	.885	.02	.878	.08	.601	.05	.721
Anterior body	.02	.734	.01	.971	.13	.370	-.09	.497
Posterior body	.03	.623	.03	.817	.08	.589	-.17	.226
Tail	.20	.009	-.30	.033	.35	.012	-.27	.034
Left PPC	.05	.392	.22	.130	-.18	.223	-.06	.643
Right PPC	.19	.009	.44	.002	-.01	.965	-.15	.250

Listed are the regression coefficients (β) and its p -values for linear relationships between $S_{\text{large}} - S_{\text{small}}$ and the predictors age, K_{max} and age* K_{max} . The coefficient of multiple determination (R^2) and its p -value are as well listed.

Table 3.

Linear relationships between $S_{\text{large}} - S_{\text{small}}$ in a given region (ROI1) and $S_{\text{large}} - S_{\text{small}}$ in another region (ROI2) with the mediator age and the covariate K_{max} (for a conceptual diagram, see Fig. 1C).

	ROI1 to age (a)		age to ROI2 (b)		ROI1 to ROI2 (c)		ROI1 to ROI2 (c')	
$S_{\text{large}} - S_{\text{small}}$	β	p	β	p	β	p	β	p
Left hemisphere								
postHC-to- anthHC	-17.8	.018	.00	.632	.19	.237	.17	.334
anthHC-to-PPC	-5.32	.410	.01	.192	-.49	.036	-.46	.050
postHC-to-PPC	-17.8	.018	.01	.081	.15	.596	.31	.287
Right hemisphere								
postHC-to-anthHC	-14.4	.048	.00	.498	.15	.317	.17	.255
anthHC-to-PPC	2.71	.698	.01	.002	-.17	.483	-.21	.356
postHC-to-PPC	-14.4	.048	.01	.004	-.21	.419	-.01	.964

Listed are the unstandardized β -coefficients and p -values for ROI1 to age (path a), the direct effect of age on ROI2 (path b), the total effect of ROI1 on ROI2 (path c) and the direct effect of ROI1 on ROI2 (path c') (postHC = posterior hippocampal ROI, anthHC = anterior hippocampal ROI, PPC = posterior parietal ROI).